PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/003685	06.04.2004	18.04.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/21, A61P31/20

Applicant
UNIHART CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6
	No:	Claims	1-5,7,8
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 The following documents are referred to in this communication:

D1 : BIAMONTI A ET AL: "Peroral alpha-interferon therapy in HPV-lesions of the lower female genital tract: preliminary results." LA CLINICA TERAPEUTICA. 2000, vol. 151, no. 1 Suppl 1, 2000, pages 53-58, XP009033655 ISSN: 0009-9074

D2 : PALOMBA M ET AL: "Oral use of interferon therapy in cervical human papillomavirus infection." LA CLINICA TERAPEUTICA. 2000, vol. 151, no. 1 Suppl 1, 2000, pages 59-61, XP009033656 ISSN: 0009-9074

D3 : DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; May 2002 (2002-05), BARNARD DALE L: "Interferon-alpha. Amarillo Biosciences." XP002288399
Database accession no. NLM12090541

D4 : WO 97/31649 A (BROZZO RENZO ; TARRO GIULIO (IT); IFI ISTITUTO FARMACOTERAPICO I (IT)) 4 September 1997 (1997-09-04)

D5 : WO 02/36072 A (BIOMEDICINES INC) 10 May 2002 (2002-05-10)

2 Document D1 discloses (the references in parenthesis applying to this document): peroral human natural alpha interferon (OROFERONE IFI) therapy in HPV-lesions of the lower female genital tract whereby dosages of 150 IU twice daily for 30 days were used, namely by putting in the oral cavity the phialoid contents of the preparation (p. 54, col. 1, par. 3).

2.1 INDEPENDENT CLAIM 1
As can be seen from the above and since phials are used to be filled with liquid compositions, document D1 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3 Document D2 discloses (the references in parenthesis applying to this document): oral interferon (OROFERONE IFI) in cervical human papillomavirus infection with or

without cervical intraepithelial neoplasia by administration of low doses (150 IU tid for 8 weeks)(p. 60, col. 1, par. 4-5).

3.1 INDEPENDENT CLAIM 1
The remarks directed to claim 1 in view of D1 apply *mutatis mutandis* for D2.

4 Document D3 discloses low-dose oral interferon-alpha (IFNalpha; Veldona) as a potential treatment for primary Sjogren's syndrome, oral mucositis in cancer patients, hepatitis B and C virus (HBV and HCV) infections, and bone marrow disorders as well as oral papillomavirus and Behçet's disease.

4.1 INDEPENDENT CLAIM 1
As can be seen from the above, document D3 seems to disclose in combination all the features defined in independent claim 1. Since only the abstract is available for the time being, no final conclusion as to novelty can be made.

5 INVENTIVE STEP

5.1 Document D4 discloses (the references in parenthesis applying to this document): use of natural human alpha-interferon in a liquid form with a concentration of 100 to 500 IU/ml, preferably in mono-dosage units, against viral infections, especially hepatitis (p. 3, l. 5 - p. 4, l. 30).

5.2 Document D5 claims the use of an interferon eg. interferon-alpha, in a formulation for short-term or long-term administration in various immunologic or proliferative diseases such as condyloma accuminata or laryngeal papillomatosis, delivered by many means, also orally (p. 14-16).

5.3 Documents D1 and D2 are considered to represent the most relevant state of the art.

5.4 In case of novelty the following applies:
The problem to be solved by the present invention may therefore be regarded as finding alternative solutions to the proposed oral administration of low doses of alpha-interferon in order to reduce side effects and to allow for complete elimination of the virus.

5.5 In view of D1 and D2 the solution proposed in claims 1-8 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) since exactly the same solution is already disclosed.

5.6 In addition, D4 proposes formulations in a liquid form with the same concentrations and in dosage units of small volumes which is the preferred solution in the present application. D4 being for administration in the treatment of hepatitis could readily be combined with D5, disclosing many other diseases treatable by interferon. Therefore the features disclosed in D4 and D5 would be combined by the skilled person, without exercise of any inventive skills in order to solve the problem posed. The proposed solution in claims 1-8 thus cannot be considered inventive (Article 33(3) PCT).

5.7 DEPENDENT CLAIM 6
Novel dependent claim 6 does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step (Article 33(3) PCT).

6 For the assessment of the present claims 1-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.